Statistical Analysis Plan

Detailed Title:	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 64 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).
eTrack study number and Abbreviated Title	208833 (STAPH AUREUS BIOCONJ-001 STG)
Scope:	All analyses for the primary and secondary objectives of the study. The analysis details for exploratory tertiary objectives are described in a separate EAP (Exploratory Analysis Plan).
Date of Statistical Analysis Plan	Amendment 5 Final: 31 Jul 2023

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3 June 2019)

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
EAP	Exploratory Analysis Plan
ES	Exposed Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HR	Hazard Ratio
ICF	Informed Consent Form
CCI	[redacted]
iSRC	Internal Safety Review Committee
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
NA	Not Applicable
PD	Protocol Deviation
pIMD	Potential Immune-Mediated Disease
PoP	Proof of Principle
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System
SD	Standard Deviation
SRT	Safety Review Team
SSTI	Skin and Soft Tissue Infection
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULN	Upper Limit of the Normal range

1. DOCUMENT HISTORY

Date	Description	Protocol Version
04 JUN 2020	First version	Version 01, dated 03 JUN 2020
03 JUN 2021	Amendment 1 (alignment to protocol amendment and other minor changes)	Amendment 02, dated 02 APR 2021
11 MAR 2022	Amendment 2 (alignment to protocol amendment and other minor changes)	Amendment 04, dated 30 NOV 2021
30 MAY 2022	Amendment 3 (Modifications in interim analysis SAS codes and operational procedure)	Amendment 04, dated 30 NOV 2021
17 OCT 2022	Amendment 4 (alignment to protocol amendment 6 and addition of elimination codes)	Amendment 06, dated 06 OCT 2022
31 Jul 2023	CCI [redacted]	Amendment 06, dated 06 OCT 2022

2. OBJECTIVES/ENDPOINTS

This SAP describes all analyses for the primary safety and secondary efficacy objectives of the study, as reported in the table below (Table 1). The statistical analysis plan for the tertiary study objectives will be provided in a separate document (Exploratory Analysis Plan).

Table 1 Primary and secondary objectives and related endpoints of the study

Objectives	Endpoints
Primary	
Descriptive: • To assess safety and reactogenicity of investigational *S. aureus* vaccine	• Occurrence and intensity of solicited local and general AEs during 7 days after each dose (i.e. day of vaccination and the 6 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days after each dose (i.e. day of injection and the 29 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of all SAEs in all subjects by vaccination group: – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366.

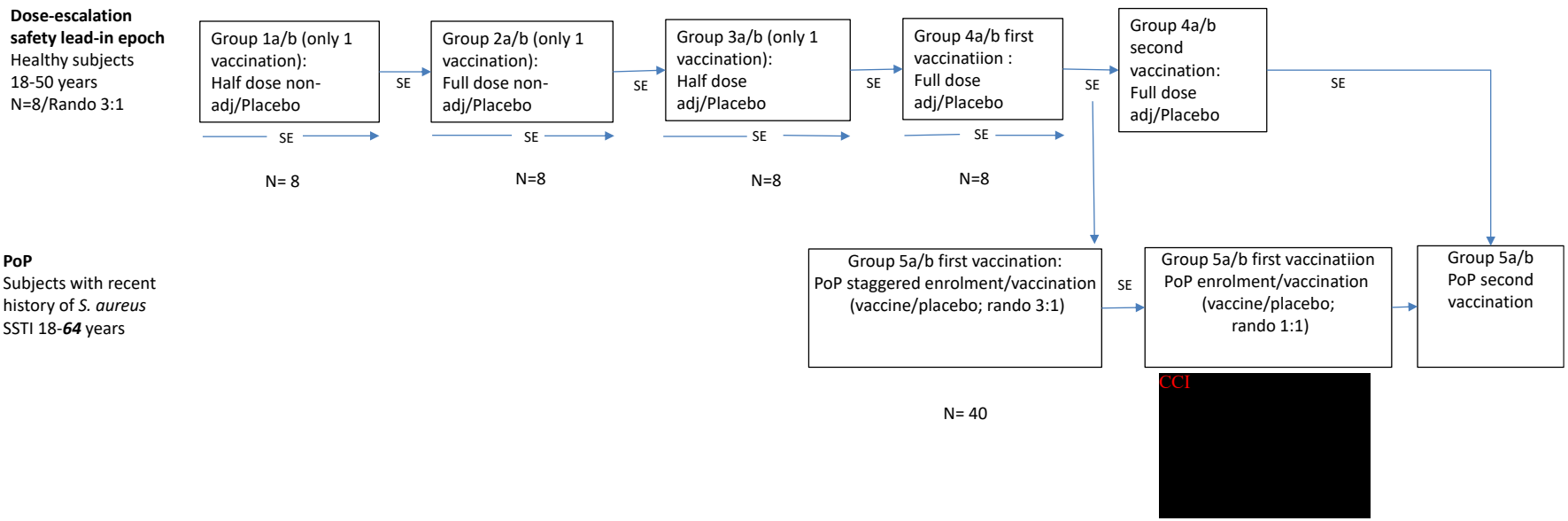
Objectives	Endpoints
	– Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence, intensity and relationship to vaccination of all potential immune-mediated disease (pIMDs) in all subjects by vaccination group: – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence of haematological and biochemical laboratory abnormalities, and changes from the baseline values after vaccination: – In all subjects of Groups 1 to 3 on Day 8. – In all subjects of Group 4 on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively. – Subjects in Group 5 Step 1 (i.e. first 40 subjects enrolled in the PoP) on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively.
Secondary	
Confirmatory: • To evaluate vaccine efficacy (VE) in the prevention of recurrent culture confirmed *S. aureus* SSTIs compared to placebo	• Key secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 75 (i.e.14 days after the second dose) up to 12 months after the second dose • Secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 15 (i.e. 14 days after the first dose) up to 12 months after the second dose

Source: Modified from Table 10 of STAPH AUREUS BIOCONJ-001 STG protocol amendment 2, dated 02 April 2021
AE = Adverse Event; pIMD = potential Immune-Mediated Disease; SAE = Serious Adverse Event; SSTI = Skin and Soft Tissue Infection; VE = Vaccine Efficacy;

3. STUDY DESIGN

The study is divided in two phases: a first dose-escalation safety lead-in phase and then a Proof of Principle (PoP) phase. Figure 1 presents a high-level overview of the whole study design. More detailed figures are provided in the respective subsections for dose-escalation safety lead-in (Figure 2) and PoP (Figure 3).

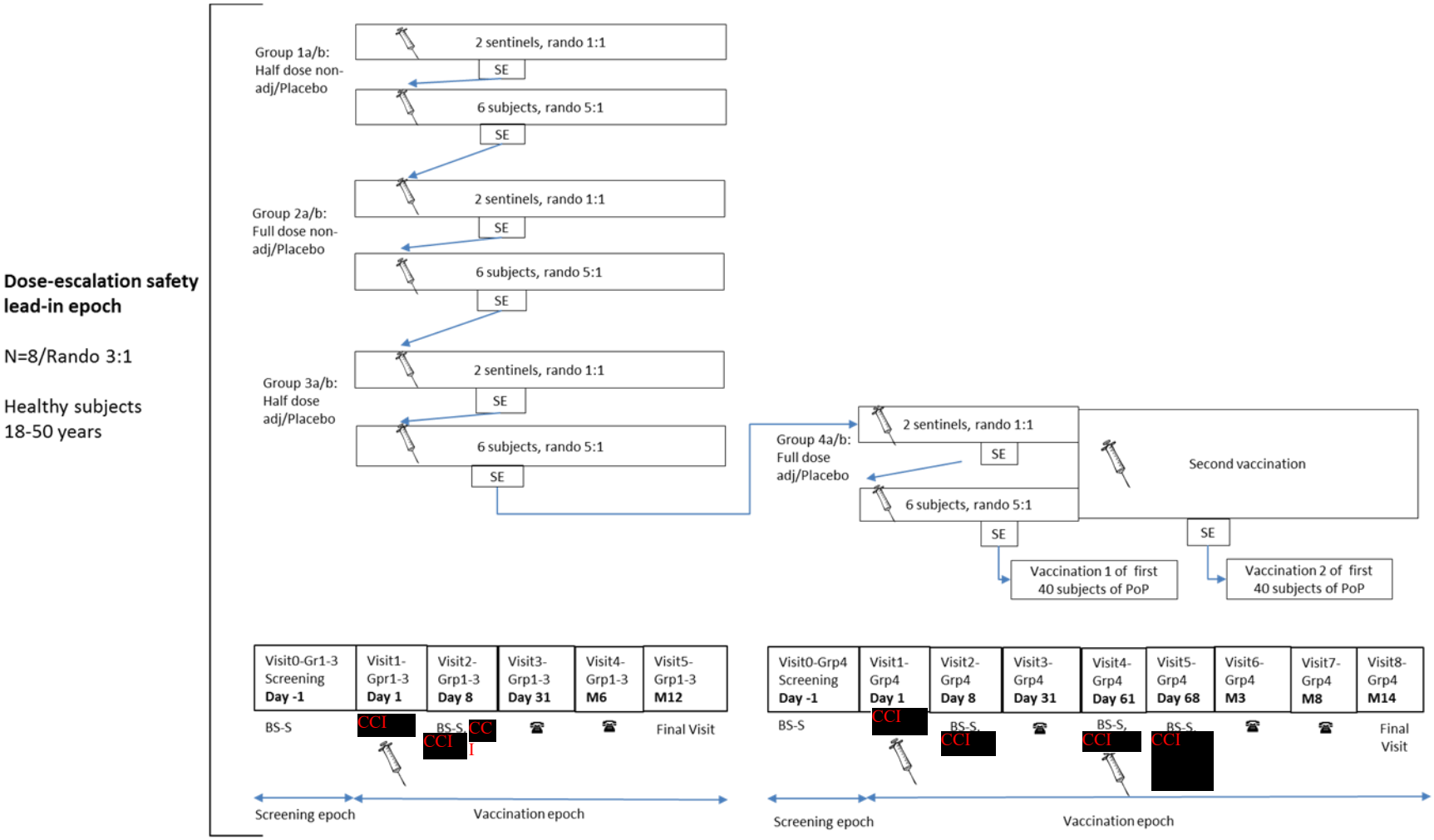
Figure 1 Overall design



adj = adjuvanted
Grp = Group
a/b = vaccine/placebo
Rando = Randomisation
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review)
PoP = Proof of Principle

Dose-scalation safety lead-in healthy subjects

Figure 2 Study design overview dose-escalation safety lead-in healthy subjects Groups 1-4a/b



CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
Grp = Group
a/b = vaccine/placebo
adj = adjuvanted
Rando = Randomisation
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review) for details refer to Section 8.6.6 in the Study Protocol
PoP = Proof of Principle
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation

CCI

- **Vaccination schedule(s):**
  - **Group 1 Half dose non-adjuvanted** (first group), 2 parallel groups:
    - **Group 1a Half dose non-adj**.: 1 dose of Sa-5Ag half dose, non-adjuvanted at Day 1
    - **Group 1b Placebo**: 1 dose of placebo (saline) at Day 1
  - **Group 2 Full dose non-adjuvanted** (second group), 2 parallel groups:
    - **Group 2a Full dose non-adj**.: 1 dose of Sa-5Ag full dose, non-adjuvanted at Day 1
    - **Group 2b Placebo**: 1 dose of placebo (saline) at Day 1
  - **Group 3 Half dose adjuvanted** (third group), 2 parallel groups:
    - **Group 3a Half dose adj**.: 1 dose of Sa-5Ag half dose, adjuvanted at Day 1
    - **Group 3b Placebo**: 1 dose of placebo (saline) at Day 1
  - **Group 4 Full dose adjuvanted** (fourth group), 2 parallel groups:
    - **Group 4a Full dose adj**.: A series of 2 doses of Sa-5Ag full dose, adjuvanted (*S. aureus* candidate vaccine, target vaccine formulation) given approximately 2 months apart (Days 1 and 61)
    - **Group 4b Placebo:** A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)

- **Safety monitoring:**

For each group in the dose-escalation safety lead-in, a staggered enrolment of 8 subjects is planned as follows: 1 vaccinated subject + 1 subject receiving placebo (sentinel subjects) followed by 5 vaccinated subjects + 1 subject receiving placebo after safety assessment of safety data collected up to Day 8. The 2 sentinel subjects in each group should be vaccinated on 2 different days.

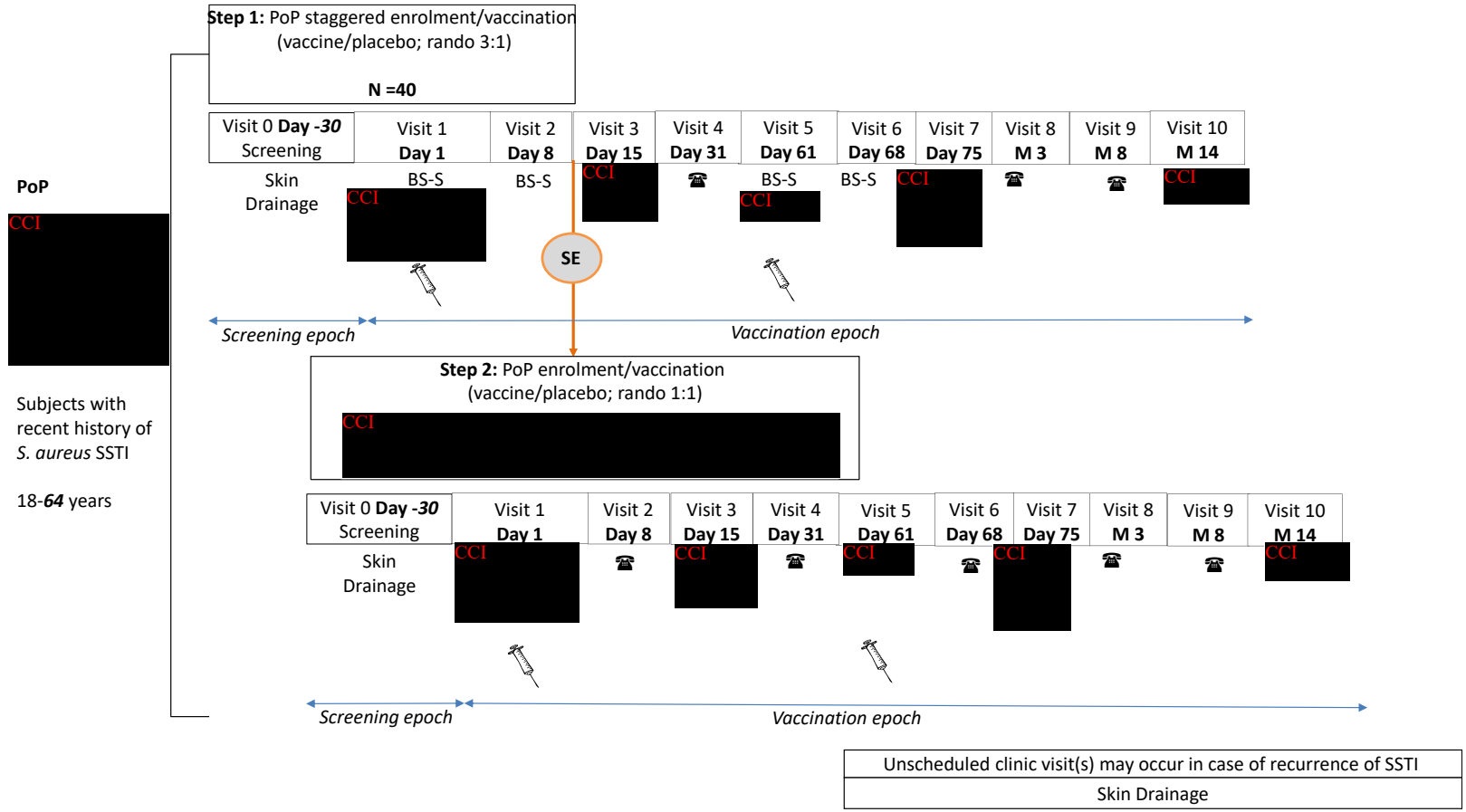
The fourth group (Full dose adjuvanted) will receive a second vaccine/placebo dose with an interval of approximately 2 months and subjects of all the groups will be followed until study end (i.e. for 12 months after last vaccination for each subject).

The investigator is not permitted to start the administration of Dose 1 for the next group and Dose 2 in the fourth group until receipt of the favourable outcome of the safety evaluation.

During the whole study period, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs). Please, refer to section 8.6 of the study protocol for detailed description of holding rules and safety monitoring.

PoP in subjects with recent *S. aureus* SSTI

Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI



Note: CDISC is not calculating with Day 0, i.e. interval between Day –30 and Day 1 is 30 days.

a/b = vaccine/placebo
SE = Safety evaluation by iSRC (unblinded), for details refer to Section 8.6.6 in the Study Protocol
PoP = Proof of Principle
SSTI = Skin and Soft Tissue Infection
Rando = Randomization
Vac = Vaccine
Plac = Placebo
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation

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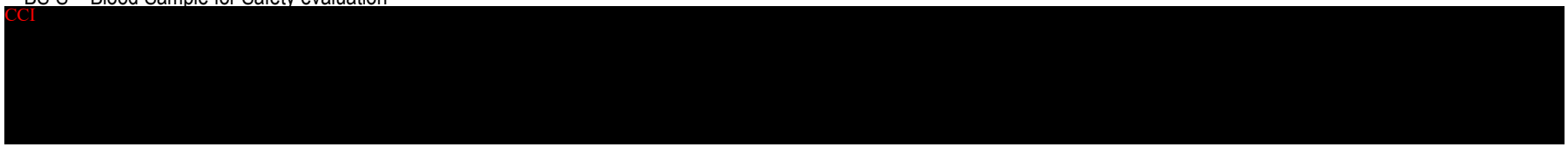


- **Vaccination schedule(s):**
  - **Group 5a Vaccine:** A series of 2 doses of *S. aureus* candidate vaccine (Sa-5Ag full dose adjuvanted) given approximately 2 months apart (Days 1 and 61)
  - **Group 5b Placebo:** A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)
- **Safety monitoring:**

The enrolment and vaccination in the PoP phase will also follow a staggered approach. After safety assessment of the first vaccination of the first approximately 40 subjects (randomised with a 3:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group) the full enrolment of the remaining subjects in the PoP phase will continue. The remaining subjects will be randomised with a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group.

Safety of the subjects in the PoP vaccination epoch will be monitored for the entire duration of the study with an overall duration of participation for each subject of approximately 14 months (i.e. 12 months after last vaccination).

For both, PoP staggered enrolment/vaccination and the PoP full enrolment/vaccination, the investigator is not permitted to start the administration of Dose 1 for the next group and Dose 2 until receipt of the favourable outcome of the safety evaluation.

During the whole study period, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs). Please, refer to section 8.6 of the study protocol for detailed description of holding rules and safety monitoring.

4. ANALYSIS SETS

4.1. Definition

Table 2 Definition of the analysis sets

Analysis Set	Description
Screened	All subjects who were screened for eligibility
Enrolled	All subjects who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). The allocation in a group will be done in function of the randomized intervention; non-randomized subjects will be part of a “Non randomized” group. Note: screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (met eligibility but ultimately not enrolled) are excluded from the Enrolled analysis set as they did not enter the study.
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full Analysis Set (FAS)	All subjects who received at least 1 dose of the study treatment and have post-vaccination efficacy data
Modified Full Analysis Set (mFAS)	All subjects who received full study treatment course to which they are randomised and have post-vaccination efficacy data

Analysis Set	Description
Per Protocol (PP)	All subjects who received full study treatment course to which they are randomised and have post-vaccination efficacy data (mFAS) minus subjects with protocol deviations that lead to exclusion from PP
Unsolicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data in the period beginning 30 minutes after vaccination until 7 days after the vaccination.
Solicited Safety 30m	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data during a period of 30 minutes after the vaccination
Overall Safety Set	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data including 30 minutes after vaccination and during a period of 7 days from the vaccination and/or report unsolicited AEs/report not having unsolicited AEs

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each set.

4.2.1. Elimination from Exposed Set (ES)

Table 3 Elimination codes from ES

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800	Fraudulent data	All
900	Invalid informed consent	All
1030	Study vaccine not administered at all	All

4.2.2. Elimination from Full Analysis Set (FAS)

All the elimination codes used for the ES are applicable and in addition the code:

- 1500a (Drop out before 14 days after first vaccination of the PoP phase)
- 1501a (No drainage sample for culture collected for recurrence of SSTI post first vaccination-PoP phase)

4.2.3. Elimination from modified Full Analysis Set (mFAS)

All the elimination codes used for the ES are applicable and in addition the codes:

- 1500b (Drop out before 14 days after second vaccination of the PoP phase)
- 1501b (No drainage sample for culture collected for recurrence of SSTI post second vaccination-PoP phase)
- 1070a (Incomplete treatment course).

4.2.4. Elimination from Per-protocol analysis Set (PPS)

All the elimination codes used for the mFAS are applicable and in addition the codes reported in the Table below.

Table 4 Elimination codes from PPS

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
1040	Administration of concomitant vaccine(s) forbidden in the protocol	All
1050	Randomisation failure (e.g., subject assigned to wrong stratum, subject randomized out of order)	All
1060	Randomisation code was broken (study blinding/unblinding procedures)	All
1070	• Study treatment not administered per protocol: – wrong route; – correct treatment administered but not compatible with treatment regimen associated to treatment schedule; – wrong treatment/replacement administered; – treatment administered with a *Staph aureus* infection ongoing – Study treatment not prepared as per protocol (e.g. reconstitution)	All
1080	Vaccine temperature deviation	All
1090	Expired vaccine administered	All
2010	Eligibility criteria not met	All
2040	Administration of concomitant medication(s) forbidden in the protocol	All
2050	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication – forbidden medical condition	All
2060	Not withdrawn after developing withdrawal criteria other than prohibited concomitant vaccination/medication -– infection related to the vaccine	All
2080	Subjects did not comply with the vaccination schedule	All

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
2120	Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results, wrong sample labelling)	All
2130	testing performed on samples not aligned with ICF; Subjects bled but not supposed to be bled	All

4.2.5. Elimination from unsolicited and solicited safety set

4.2.5.1. Unsolicited Safety Set

All the elimination codes used for the ES are applicable and in addition the code 1150.

Code 1150 will be attributed to subjects if all the following conditions are met:

- subject did not return for visit/perform phone contact on Day 8 and Day 68 (only for groups 4 and 5)
- subject did not complete the eDiary;
- subject did not perform the scheduled phone contact 30 days after vaccinations;
- subject did not return for the visit scheduled 12 months after last vaccination and did not perform the phone contact scheduled 6 months after last vaccination;
- subject did not report any unsolicited AE.

4.2.5.2. Laboratory Safety Set

The analysis for haematology and biochemistry parameters will be performed on a subset of the Unsolicited Safety Set. All the elimination codes used for the Unsolicited Safety Set are applicable and in addition the code:

- 2100 (no safety serological results available)
- 2110 (incorrect or expired sample tube used for sample type-safety blood draw)

An additional analysis excluding subjects with safety blood samples out of window will be performed (elimination code for the specific analysis: 2090 applicable to V2 for groups 1-3, V2, V5 for group 4 and V2, V6 for group 5).

Note: in the PoP phase, subjects in Step 2 are not included in this set.

4.2.5.3. Solicited safety set

All the elimination codes used for the ES are applicable and in addition the code:

- 1160 (no post-vaccination solicited safety data excluding30 minutes, during 7 days of follow up)
- 1161 (post-vaccination solicited safety data excluding 30 minutes, during 7 days of follow up not reported according to GCP)

4.2.5.4. Solicited safety set 30m

All the elimination codes used for the ES are applicable and in addition the code:

- 1160b (no post-vaccination solicited safety data during 30 minutes after the vaccination)

4.2.5.5. Overall Safety Set

All subjects who are in the Solicited Safety Set 30m and/or in the Solicited Safety Set and/or in the Unsolicited Safety Set (code 2150 for subjects with no safety follow up beyond the day of vaccination).

Subjects will be analysed as "treated" (i.e., according to the vaccine a subject received rather than the vaccine to which the subject may have been randomized).

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and statistical methods are described in section 9 of this document.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics (age at first study vaccination in years, gender, race and ethnicity), SSTIs history (PoP only), will be summarised by overall and vaccine groups using descriptive statistics:

- Frequency tables will be generated for categorical variables such as centre.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height, weight and body mass index (BMI).

Withdrawal status will be summarized by group using descriptive statistics:

- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal (specifying if there is any relationship with COVID-19.)
- The number of subjects enrolled into the study as well as the number of subjects excluded from the per protocol set (PPS) and mFAS will be tabulated.

5.1.2. Additional considerations

Demographic characteristics will also be summarized on Enrolled Set for web public disclosure.

Vital signs will be summarized by vaccine group using descriptive statistics at all timepoint(s) the information is collected on Exposed Set and modified Full Analysis Set.

Summary of important protocol deviations leading to elimination will be tabulated by vaccine group and by relationship with COVID-19. An individual listing will also be provided.

Summary of medical history will be performed on Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) and Preferred Term.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

Any impact of COVID-19 on subjects' exposure will be tabulated by vaccine group.

5.2.2. Additional considerations

The number and percentage of subjects who received study vaccine doses will be tabulated for each study group (based on the ES).

5.3. Efficacy/Effectiveness

5.3.1. Analysis of efficacy planned in the protocol

The efficacy analysis will be based on the mFAS. A supplementary analysis will be based on the PPS.

Rules for SSTI cases:

- All cases of SSTI will be reported, including multiple cases in the same subject.
- The start date of a case is the date of the visit during which the diagnosis is done by a treating physician or equivalent licensed medical professional or based on medical records review by a study physician.

- A new SSTI episode may be assessed by a study physician at site for any SSTI visit occurring after the clinical resolution of the previous SSTI and, if it does not represent a persistence of the previous episode as per medical judgement, it can be considered a new episode.

Table 5 Statistical analysis methods for the secondary study objectives

Endpoint	Statistical Analysis Methods
Key secondary	The analysis of efficacy will be based on the occurrence of the first case of SSTI anytime from 14 Days after the administration of the second dose of the study vaccine up to 12 months. All subjects from the mFAS will contribute to the comparison between the treatment and the placebo groups. Time to occurrence of key secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio Vaccine (VE) will be defined as 1 minus the hazard ratio times 100: VE = (1 – hazard ratio) x 100 Censoring will occur at the time of the last scheduled or medically attended visit without the occurrence of SSTI cases before the end of follow up. Subjects who will complete the follow up without events will be censored at 1 year. In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 1.61% at the interim analysis and 5.89% at the final analysis. The objective will be met if the 1-sided P-value calculated for the null hypothesis H0 = [occurrence SSTI VE = 0%] is lower than defined 1-sided alpha level.
Co-secondary	The co-secondary endpoint will be analysed only if the statistical significance is demonstrated for the key secondary endpoint. For this analysis, the FAS will account for the first case of SSTI anytime from 14 Days after the administration of the first dose of the study vaccine up to 14 months. Time to occurrence of the co-secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio. In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 5.89%. (the nominal alpha level is equal to the key secondary at the final analysis, because we use a sequential procedure). The objective will be met if the 1-sided P-value calculated for the null hypothesis H0 = [occurrence SSTI VE = 0%] is lower than defined 1-sided alpha level. If statistical significance for key secondary endpoint is not demonstrated, a descriptive analysis of co-secondary endpoint will be provided.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

5.4. Immunogenicity

5.4.1. Analysis of immunogenicity planned in the protocol

Not in the scope of this SAP

5.4.2. Additional considerations

Not applicable

5.5. Analysis of safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

The primary analysis will be performed on the Solicited Safety and Unsolicited Safety sets.

Table 6 Statistical analysis methods for the primary study objectives

Endpoint	Statistical Analysis Methods
Primary	**Within groups assessment** The overall incidence, with exact 95% confidence intervals (CIs) of any solicited AE (local or general), of at least 1 solicited local AE and of at least 1 solicited general AE during the 7-day (Day 1-7) period will be tabulated per study group and for each dose and overall. The same calculations will be performed for solicited AEs rated as grade 3 and fever >40°C/104°F. The overall incidence, with exact 95% confidence intervals (CIs) of any unsolicited AE, unsolicited AEs by MedDRA system organ class and by preferred term during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group and after each dose and overall. The same calculations will be performed for unsolicited AEs rated as grade 3, for unsolicited AEs causally related to vaccination and for grade 3 unsolicited AEs causally related to vaccination. The number and percentages of subjects who experienced at least one SAE or any pIMD during the entire study period (Groups 1-3 Day 1-366, Groups 4 and 5 Day 1-426) will be reported. The percentage of subjects having haematology and biochemistry results below or above the normal laboratory ranges with the changes from the baseline values will be tabulated by time point for Group 1 to 4 and Group 5 Step 1. Duration will be presented. The verbatim reports of unsolicited symptoms will be reviewed by a GSK physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Event Terminology. Serious adverse events and withdrawal due to adverse event(s) will be described in detail.

5.5.2. Additional considerations

5.5.2.1. Analysis of solicited AEs

The analysis of solicited AEs will be performed on the Solicited safety set and Solicited safety set 30 m.

The following local AEs will be solicited for 7 days after each vaccination:

Table 7 Solicited local adverse events and their grading:

Local AE	Grading	Collection period
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Redness at injection site	0: < 25 mm diameter 1: ≥ 25 mm to ≤ 50 mm diameter 2: > 50 mm to ≤ 100 mm diameter 3: > 100 mm diameter	Day 1-Day 7 Day 61-Day 67
Swelling at injection site	0: < 25 mm diameter 1: ≥ 25 mm to ≤ 50 mm diameter 2: > 50 mm to ≤ 100 mm diameter 3: > 100 mm diameter	Day 1-Day 7 Day 61-Day 67

For the grading definition of Pain please refer to Table 34 of the study protocol.

The percentage of subjects with at least one local solicited AE reported in e-diary, within 7 days period after each dose, will be tabulated by group together with the exact 95% CI [Clopper, 1934]. Similarly, the percentage of doses followed by at least one local solicited AE will be tabulated together with the exact 95% CIs within each group. The same tabulation will be done for grade 3 solicited local AEs.

The following general AEs will be solicited for 7 days after each vaccination:

Table 8 Solicited general adverse events and their grading:

General AE	Grading	Collection period
Headache	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fatigue	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Nausea	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Vomiting	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Diarrhoea	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Abdominal pain	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67

General AE	Grading	Collection period
Myalgia*	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Shivering*	0: None 1: Mild 2: Moderate 3: Severe	Day 1-Day 7 Day 61-Day 67
Fever	0: < 38°C 1: 38°C to <39°C 2: ≥ 39.0°C to ≤40°C 3: > 40.0°C	Day 1-Day 7 Day 61-Day 67

*This AE will be collected as solicited during the PoP epoch (only for group 5)

For the grading definition of general solicited AEs please refer to Table 34 of the study protocol.

The percentage of subjects with at least one general solicited AE reported in e-diary within 7 days, after each dose will be tabulated by group together with the exact 95% CI.

Similarly, the percentage of doses followed by at least one general solicited AE will be tabulated together with the exact 95% CIs within each group.

The same tabulation will be done for grade 3 solicited general AEs.

The percentages of subjects reporting each individual local and general solicited AE by maximum grading during the solicited follow-up period (i.e., day of vaccination and six subsequent days after each vaccination) will be tabulated with exact 95% CIs after each dose and overall by group. The percentages of doses followed by each individual solicited local and general AE by maximum grading will be tabulated overall by group with exact 95% CIs [Clopper, 1934].

For solicited symptoms, missing or unevaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms will include only subjects/doses with documented safety data (i.e., symptom screen/sheet completed).

5.5.2.2. Analysis of unsolicited AEs, SAE and pIMD

The analysis of unsolicited AEs will be performed on the Unsolicited safety set.

All the unsolicited adverse events occurring during the study, judged either as related or not related to vaccination by the investigator, will be recorded.

The original verbatim terms used by investigators to identify adverse events in the e-CRFs will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. Adverse events judged by the investigator as at least possibly related to study vaccine will be summarized by vaccine group, according to System Organ Class (SOC) and Preferred Term (PT) within SOC. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest

relationship to the vaccine group will be counted (specifically, for dose-escalation safety lead-in).

The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA during a 30-day follow-up period after each dose (i.e. day of injection and the 29 subsequent days) will be tabulated with exact 95% CI for each group. The same tabulation will be performed by severity, by vaccination and for unsolicited AEs with a relationship to vaccination.

SAEs, deaths, pIMDs and AEs leading to withdrawal reported during the entire study will be tabulated (from Day 1 until study termination) and listed.

In addition, SAEs related to study participation or concurrent GSK medication/vaccine reported from inform consent signed until entire study duration will be also listed.

Incidence of COVID-19 reported as an unsolicited AE and SAE will be tabulated with exact 95% CI for each group.

A summary of COVID-19 assessments throughout the study will be tabulated for each group.

This study foresees one injection in groups 1-3 and two injections (i.e., two vaccinations) for each subject in groups 4 and 5, and thus unsolicited AEs summary tables will be presented overall and by period of onset and will include frequency distributions of the different adverse events.

Number and percentage of subjects with the following AEs will be computed:

Onset between the day of each injection and the 29 subsequent days after each vaccination:

- Any AE (overall)
- Any AE by vaccination
- Any AE by severity (overall) (only Grade 3 severity for dose-escalation safety lead-in)
- Any AE by severity and by vaccination (PoP only)
- Related unsolicited AEs (overall)
- Related unsolicited AEs by vaccination
- Related unsolicited AEs by severity (overall) (only Grade 3 severity for dose-escalation safety lead-in)
- Related unsolicited AEs by severity and vaccination (PoP only)
- Any medically attended unsolicited AE (overall)
- Any medically attended unsolicited AE, by vaccination
- Any related AE with onset within 7 days from vaccination with the PT code in Table 9

Onset between the Day of injection (Day 1) and Day 366 for the Groups 1-3, Day 1 and Day 426 for the Groups 4 and 5

- Any serious adverse events (SAE) (overall)
- Any serious adverse events (SAE) by vaccination
- Any serious adverse events (SAE) by severity (only Grade 3 severity for dose-escalation safety lead-in)
- Related SAE (overall)
- Related SAE by vaccination
- Related SAE by severity (only Grade 3 severity for dose-escalation safety lead-in)
- Any AE leading to death (overall)
- Any unsolicited AE leading to premature withdrawal from study (overall)
- Any potential immune mediated diseases (overall)
- Any potential immune mediated diseases by vaccination
- Any AE leading to hospitalization (overall)

5.5.2.3. Combined analysis of solicited and unsolicited AEs

The combined analysis of solicited and unsolicited AEs will be performed on the Overall safety set.

Solicited AEs will be coded by MedDRA as per the following codes:

Table 9 Solicited AE with Preferred Term

Solicited symptom	Preferred Term code	Corresponding Preferred Term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Nausea	10028813	Nausea
Vomiting	10047700	Vomiting
Diarrhoea	10012727	Diarrhea
Abdominal pain	10000081	Abdominal pain
Myalgia	10028411	Myalgia
Shivering	10008531	Chills
Fever	10037660	Pyrexia

5.5.2.4. Other safety analyses

Medications will be coded using WHODRUG dictionary.

All collected concomitant medications and vaccinations will be listed. In addition, prior and concomitant vaccinations will be summarized. In case of pregnancies during the study, follow-up data and pregnancy outcomes will be described in detail.

For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated as post-vaccination versus pre-vaccination values: Visit 2 versus screening, for all groups of the safety lead-in; Visit 2 versus Visit 1 for group 5 Step 1 of the PoP; Visit 5 versus Visit 4, for group 4 of the safety lead-in, and Visit 6 versus Visit 5, for group 5 Step 1 of the PoP.
- Post-vaccination versus pre-vaccination values (Visit 2 versus screening, for all groups of the safety lead-in; Visit 2 versus Visit 1 for group 5 Step 1 of the PoP; Visit 5 versus Visit 4, for group 4 of the safety lead-in, and Visit 6 versus Visit 5, for group 5 Step 1 of the PoP) will be tabulated according to FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", see section 10.3.

5.5.2.5. Exclusion of implausible solicited Adverse Event

Some local and general adverse events will be directly measured by the subject and will not be subject to a reconciliation process with the exception of redness and swelling over 300 mm, which will be subjected to check and reconciliation.

The plausible measurements programmed in the eDiary are summarized in the table below:

Table 10 Plausible Solicited Adverse Events

Parameter	Plausible range measurements
Body temperature	33.1°-41.9°
Redness	1 mm--899 mm
Swelling	1 mm—499 mm

6. ANALYSIS INTERPRETATION

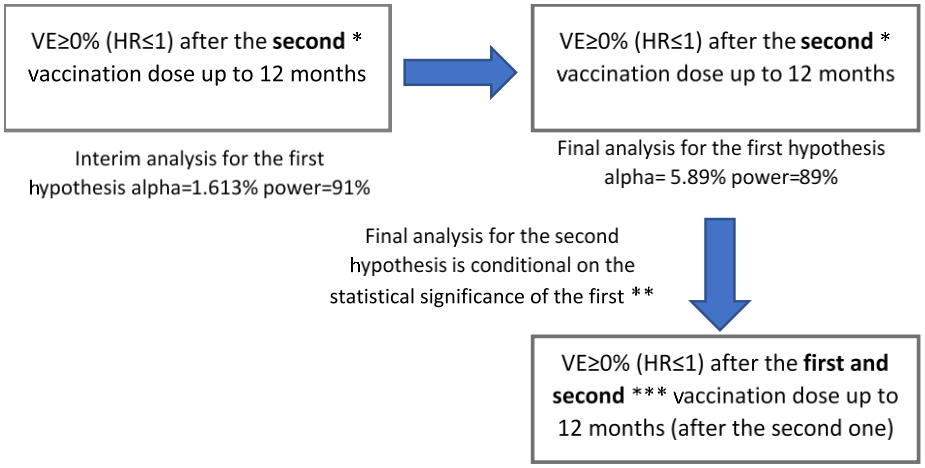
Except for analysis on efficacy objectives, with predefined success criteria and an appropriate type I error control, comparative analyses are descriptive with the aim to characterize the difference between groups.

With respect to confirmatory analyses on efficacy objectives the interpretation will be done in a hierarchical manner.

After the final analysis for the first hypothesis a sequential procedure will be used in order to control the overall type I error for the efficacy objective: starting from the first

hypothesis on the efficacy after the second dose, the second hypothesis on the efficacy after the first dose will be tested only if the efficacy after two doses will be demonstrated.

Figure 4 Sequence for evaluating both efficacy objectives in order to control the overall type I error below 7.5% (one-sided) and the power equal to 80%



*All subjects who experience an SSTI recurrence at least two weeks after the second dose. If a subject experiences an event after the first and before the second dose the case will be not considered as first event after the second dose. If a subject has an event after the first and another after the second dose, only the case after the second dose will be considered as first event after the second dose.
**The adjusted alpha for this hypothesis can only be given at the time of analysis as the adjustment is dependent on the alpha spent at the interim analysis.
***All subjects who experience an SSTI recurrence at least two weeks after the first dose.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints. If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in annex(es) to the study report.

All analyses (including interim analysis) will be conducted on clean data.

- The analyses will be performed stepwise: An interim analysis for efficacy and futility will be done when 48% of the assumed total number of culture confirmed cases of recurrent *S. aureus* SSTIs (13 events after the second dose) will be observed. The timing of the interim analysis will be according to how the data actually accrued. This analysis will be performed by an independent data analysis centre (IDAC), in order to maintain the blind to the treatment codes. An independent GSK statistician will validate the outcome of the interim analysis provided by IDAC, to check whether efficacy/futility criteria are met (more details in section 7.3)

- The main efficacy analysis and the respective conclusions on efficacy will be done on the total number of events, i.e. at 27 events after the second dose, and the enrolment is stopped. If the enrolment is stopped for efficacy or futility following the interim analysis and we do not observe planned number of 27 events by end of study (Last Subject Last Visit), we proceed to the analysis with all collected number of events.
- A second line efficacy analysis will be performed on all available efficacy data obtained up to study conclusion (1 year of follow up after the second vaccination) but this additional data (beyond 27 events) will not be taken into account for the conclusion of vaccine efficacy. The final clinical study report containing all data will be written and made available to the investigators.

Description	Disclosure Purpose
Interim analysis for efficacy and futility	Internal
Final Analysis for safety and efficacy	Public disclosure, Study report
Annex for efficacy and safety (and other tertiary endpoints)	Additional efficacy analysis with additional events and safety

7.2. Statistical considerations for interim analyses

One interim analysis for efficacy and futility will be done following a group sequential design for the key secondary efficacy analysis. The interim analysis is event driven and is planned when 48% of the assumed total number of culture confirmed cases of recurrent *S. aureus* SSTIs (13 events after the second vaccination) will be observed and it may stop the enrolment of the study for efficacy or futility.

In case of stopping for efficacy at the interim analysis, also the second secondary efficacy endpoint will be tested with the same alpha used for the first hypothesis (alpha=1.613%). Enrolment maybe stopped if the null hypothesis is rejected (efficacy) or accepted (futility) after the interim analysis, but the follow up of subjects will continue for 12 months after the second dose.

The design assumes that 2 sequential tests are made for the key efficacy objective using test boundaries (binding for efficacy and not binding for futility) calculated by the O'Brien-Fleming spending function and assuming that time to event follows an exponential distribution. An adjusted alpha equal to 1.613 % and a beta equal to 8.83% (or a power equal to 91%) will be spent at the interim to reject or accept the null hypothesis for the key efficacy objective with a sample of 13 cases. At the final analysis the adjusted alpha and beta will be, respectively, 5.89% and 11.17% (or a power equal to 89%) with a sample of 27 cases. The final alpha and beta after the two sequential tests will be kept to 7.5% and 20%. The secondary efficacy endpoint will be tested at the final analysis after rejecting the null hypothesis for the key objective.

The proc SEQDESIGN is used for the planning of the test boundaries with the code reported in the section 5.3. The output with the limits is used in the proc SEQTEST (see section 5.3.2)

7.3. Operational considerations for interim analysis

- This analysis will be performed by an independent data analysis centre (IDAC), in order to maintain the blind to the treatment codes. IDAC members will have access to the unblinded study data and will store their programs in LSAF (Life Science Analytics Framework) in a restricted area, not accessible by the study team until the end of the study.
- The study statistician and the statistical analysts will notify the IDAC when 13 culture-confirmed cases after the 2nd dose will be reached and provide the IDAC with the SAS codes for interim analysis under the anticipated statistical considerations.
- An independent GSK statistician will validate the outcome of the interim analysis provided by IDAC, to check whether efficacy/futility criteria are met. He/she will have access to the same restricted area the IDAC will have access to.
- If the obtained test statistic lies in the "Rejection Region", i.e. its value is higher than the rejection boundary value, it suggests the study meets the efficacy criteria at the interim analysis. If the test statistic lies in the “Continue Region”, i.e. its value is between the rejection and acceptance boundaries, it suggests the study should continue, If the obtained test statistic lies in the "Acceptance Region", i.e. its value is lower than the acceptance boundary value, it suggests the study meets the futility criteria at the interim analysis (non binding criteria).

8. CHANGES FROM PLANNED ANALYSES

Not applicable

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

Not applicable

9.2. Statistical Method

Not applicable

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules) of this document, if any.

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one. If the flag indicating whether the event occurred before or after vaccination is missing then "after vaccination" is imputed and relative dose is assigned accordingly.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 1
- A missing day and month will be replaced by January 1st

The following exceptions apply:

- Birth dates:
  - A missing day will be replaced by 15
  - A missing month will be replaced by June 30th
- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected or the flag is missing, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be first day of that month.

- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected or the flag is missing, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

Haematology/chemistry laboratory data requiring grading as per FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials may have more decimals than expected or may require conversion to the unit associated to the grade, leading to more decimals than expected.

In order to determine the grading, the following rule will be used

1. In case a conversion is needed, the original results will be used for the conversion without a previous rounding.
2. In case an approximation is needed to determine the grading, the result (or the result divided by the upper limit of the normal range (ULN), depending on the test) expressed in the expected units will be rounded to the number of decimals used for the grading.

If the original result is expressed as < x or > x, then, for grading purpose, it is imputed to x and converted to expected units, if needed.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

As the study foresees the use of electronic diaries for the collection of solicited adverse events, a solicited adverse event will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical output.

10.1.3. Data derivation

10.1.3.1. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.2. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

10.1.3.3. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.4. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.5. Numerical serology results

Not applicable

10.1.3.6. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

10.1.3.7. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated from the first day of occurrence to last day of occurrence with the adverse event reported at grade 1 or higher during the solicited adverse event period.

10.1.3.8. Counting rules for combining solicited and unsolicited adverse events

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.9. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

  - The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
  - Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height/weight variables will be displayed with no decimals.

The maxima and minima of transformed body temperatures will be displayed with one decimal.

10.1.4.4. Serological summary statistics

Not applicable

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen [Miettinen, 1985].

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

10.3. FDA toxicity grading scales for haematology/ biochemistry parameters

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

CCI

CCI
[redacted]

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